MODERATE ALTITUDE AND MYOCARDIAL ISCHEMIA AND INFARCTION

by

Rebecca Rector Rice

A thesis submitted to the faculty of
The University of Utah
in partial fulfillment of the requirements for the degree of

Master of Science

College of Nursing

The University of Utah

June 1982

THE UNIVERSITY OF UTAH GRADUATE SCHOOL

SUPERVISORY COMMITTEE APPROVAL

of a thesis submitted by

Rebecca Rector Rice

This thesis has been read by each member of the following supervisory committee and by majority vote has been found to be satisfactory.

Chairman: Maeona K. R.N., Ph.D.

Marjorie Cengiz, R.N., M.S.

Guy Zimmerman, M.D.

THE UNIVERSITY OF UTAH GRADUATE SCHOOL

FINAL READING APPROVAL

To the Graduate Council of The University of Utah:

I have read the thesis of Rebecca Rector Rice in its final form and have found that (1) its format, citations, and bibliographic style are consistent and acceptable; (2) its illustrative materials including figures, tables, and charts are in place; and (3) the final manuscript is satisfactory to the Supervisory Committee and is ready for submission to the Graduate School.

[illegible] [illegible]., M.S.
Member, Supervisory Committee

Approved for the Major Department

[illegible]
Linda K. Amos, Ed.D., F.A.A.N.
Chairman, Dean

Approved for the Graduate Council

[illegible]

ABSTRACT

This study compared visitors to a moderate altitude (1,829 m to 3,100 m) hospitalized with myocardial ischemia and/or infarction to hospitalized residents of that moderate altitude with similar diagnoses. The purpose was to quantify, describe and compare visitor and resident characteristics and hospital courses in order to determine whether a relationship existed between the severity of myocardial ischemia and/or infarction occurring at moderate altitude and the altitude of residence.

The study group consisted of 112 patients admitted to the Intensive Care-Coronary Care Unit of a 64 bed rural hospital with either myocardial ischemia or myocardial infarction. The study design was an ex-post facto chart review for a 36 month period.

Subjects were divided into two groups of either visitors or residents of the study area. These two groups were further subdivided into subjects with ischemia and subjects with infarction. Data on numerous variables was collected from the medical record.

Using an independent student t-test and chi-square

statistic no relationship was found between the severity of ischemia or infarction and the altitude of residence. There were no significant differences during hospitalization between visitors and residents in complications, length of hospitalization or length of supplemental oxygen usage.

Based on a Spearman Rho correlation and independent student t-test, findings do suggest that altitude may affect physiologic response to ischemia or infarction. Visitors tended to have more frequent ventricular tachycardia and sinus bradycardia and higher admission blood pressures.

Prior to hospitalization altitude may have affected visitors' abilities to compensate for an ischemic event. This is suggested by the findings that a larger percentage (46%) of the visitor population was diagnosed with myocardial infarction than was the resident group with only 30% diagnosed with infarction.

CONTENTS

LIST OF TABLES

ACKNOWLEDGMENTS

I wish to thank the members of my supervisory committee, Dr. Maeona Jacobs, Marjorie Cengiz, R.N., M.S., and Dr. Guy Zimmerman for their knowledge and assistance, Sandra Haak, R.N. for her encouragement and my family for their enthusiasm and support in this effort.

CHAPTER I

INTRODUCTION

Life at high altitude exposes man to a hypoxic environment with a diminished availability of oxygen to tissue. As man ascends from sea level, atmospheric pressure decreases with a proportional fall in the partial pressure of oxygen (pO_2) in ambient air. The resulting decrease in inspired, alveolar and arterial pO_2 modifies all steps in oxygen transport (Lenfant & Sullivan, 1971). This initiates physiologic changes, primarily cardiopulmonary, to improve tissue oxygenation.

Physiologic changes occur in both visitors and residents of altitude environments. However, the goals of these changes differ (Houston, 1980). The adjustments seen in visitors are an attempt to maintain a normal supply of oxygen to cells through mechanisms such as hyperventilation and increased heart rate which cause a secondary increase in energy expenditure and oxygen utilization. Acclimatization of residents results primarily in a more efficient use of the chronically decreased supply of ambient oxygen.

Thus differences between visitors and residents have implications for the response to any cardiopulmonary illness occurring at altitude. Since residents have a more optimal balance between oxygen supply and demand through acclimatization mechanisms they may be able to respond more adequately to illness.

Coronary artery disease, the major health problem in the United States (Braunwald & Sobel, 1980) will be manifested by at least some visitors and residents of altitude as myocardial ischemia and infarction. Since the severity of myocardial ischemia and infarction depends partially on the ability to improve the balance between oxygen supply and demand (Braunwald & Maroko, 1974; Sobel & Shell, 1973), the altitude resident may experience fewer complications and have a better prognosis following this illness.

Rationale for Study

For centuries it has been known that respiratory difficulties occur at high altitude (Heath & Williams, 1977) and extensive literature exists concerning the effects of altitude on man. However, almost all research concerns the effects of high altitudes above 3,100 m on healthy persons, often young, well conditioned athletes. This is not the typical setting for most interaction between man and altitude and the direct appli-

cability of such research is limited. Little is known about the increasingly common situation of visitation or residence at moderate altitudes of 1,600 m to 3,100 m by persons of all ages with differing states of health and physical conditioning.

Due to an increasing interest in outdoor recreation, an increase in travel and a growth in the state and national park system (King, 1968), the potential population at moderate altitudes has increased. Since visitors and residents differ in certain physiologic mechanisms it is essential that the health care provider understand physiologic factors unique to these areas.

Since altitude exposure causes changes in oxygen transport a common but serious illness such as coronary artery disease with myocardial ischemia and infarction in which oxygen transport is compromised should be of interest to researchers. Although adjustments and acclimatization to moderate altitudes may be subtle, when superimposed on ischemia and infarction these may have importance in a patient's ability to respond adaptively. Consequently, more data is necessary to predict the course and treatment of this illness at moderate altitude.

Nursing Concern

Anticipation and prediction of patient problems,

basic to nursing, can only result from a thorough understanding of physiology. Through this understanding, early assessment and intervention are possible to prevent complications of illness and promote adaptation and health.

Four areas of nursing will benefit from data on the physiologic effects of altitude when superimposed on myocardial ischemia and infarction. Since preservation of ischemic myocardium decreases complications and improves prognosis (Sobel, 1980; Sobel, Bresnahan, Shell, & Yoder, 1972) nurses in all areas could initiate interventions which would improve a patient's oxygen supply and demand balance and, therefore, promote health.

These four areas of nursing include:

1. Patient health educators who could counsel patients planning visits to moderate altitude environments to modify their speed of travel and activity in order to decrease oxygen demands at altitude,

2. Nurse practitioners functioning as the initial health care provider in rural, isolated mountainous areas who could initiate early, aggressive intervention,

3. Critical care nurses in altitude hospitals who could care for patients with life-threatening physiologic crises within a broader physiologic framework, and

4. General duty nurses in altitude hospitals caring

for post-myocardial ischemia and infarction patients who, by understanding the possible increased vulnerability of altitude visitors, could provide more optimal care.

Conceptual Framework

Through understanding the Conceptual Model in Figure 1 nurses can choose to intervene at various points within the model to modify complications and decrease the severity of myocardial ischemia and/or infarction. The interrelationships between altitude exposure, visitors' adjustments and residents' acclimatization and myocardial ischemia and/or infarction are depicted. These interrelationships are based primarily on research conducted at high altitude. However, the Conceptual Model suggests that similar relationships may exist at moderate altitude with the postulated effects on myocardial ischemia and/or infarction.

All events in this model occur within a hypoxic, altitude environment (1). Since man is an open system that interacts with the environment the hypoxia of altitude will modify all events and responses depicted in this model.

The large circle represents the disease states of coronary artery disease (2). Cellular hypoxia (3a) and diminished coronary blood flow (3b) results from coronary artery disease. If these decrease below levels

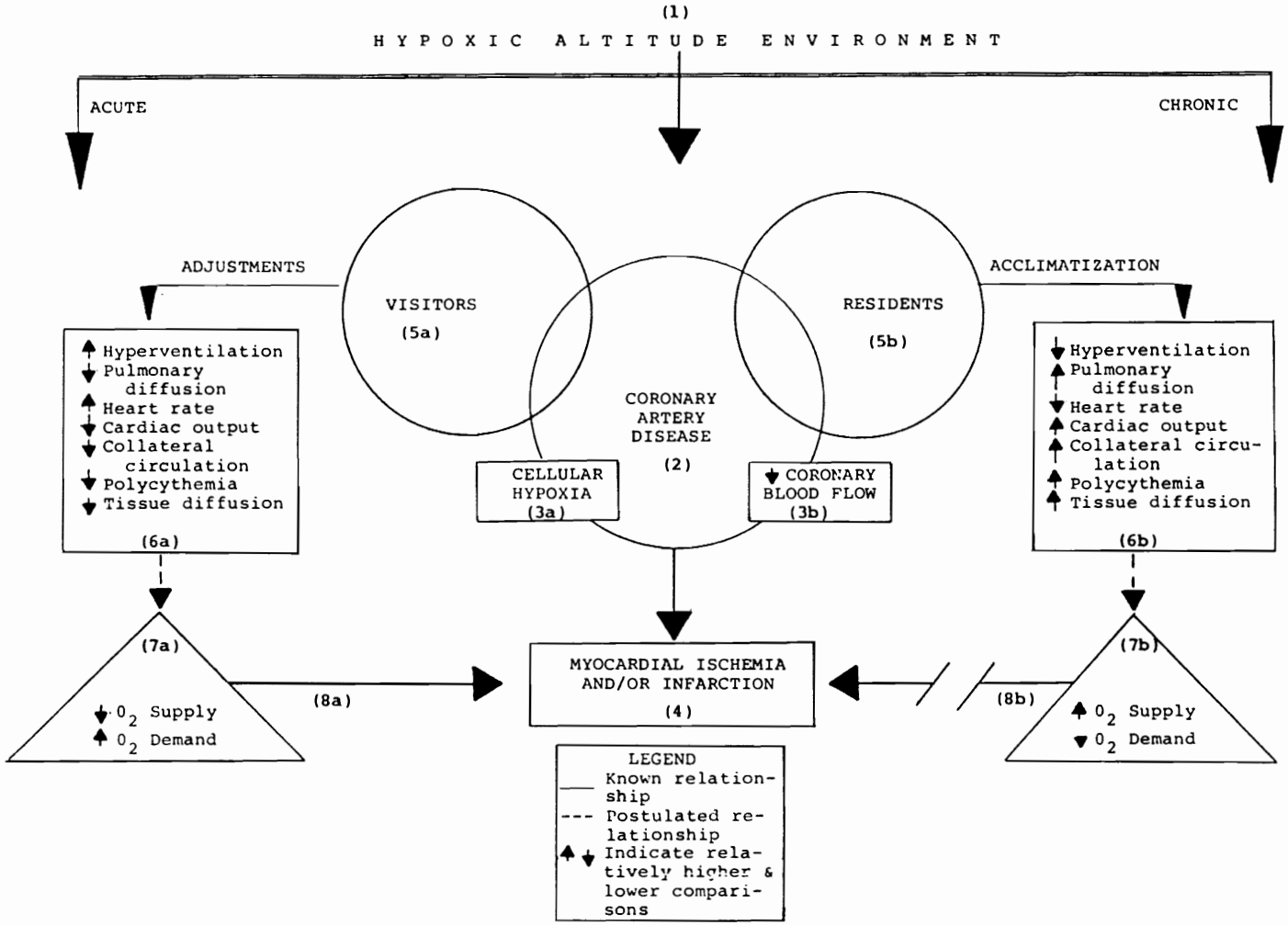

Figure 1. Conceptual model of relationships between altitude and myocardial ischemia and/or infarction.

necessary to meet myocardial needs myocardial ischemia and/or infarction (4) occur.

The small circles represent visitors (5a) and residents (5b) in this hypoxic, altitude environment. Both the visitor population and the resident population will have members with coronary artery disease indicated by the overlap of circles (2) and (5a) and (2) and (5b).

There are physiologic differences between visitors and residents resulting from acute adjustments or chronic acclimatization in a hypoxic, altitude environment. These mechanisms are listed in the large squares (6a & 6b). The small arrows in (6a) and (6b) indicate how visitors and residents differ when compared to each other.

In comparison to residents, square (6a) indicates that visitors have a higher oxygen demand due to the energy required to maintain a greater ventilation and heart rate. Although the purpose of these mechanisms is to improve oxygen supply they are not completely successful as pulmonary diffusion, cardiac output and tissue diffusion are below residents' values. Furthermore, visitors lack the ability of residents to increase their oxygen supply through collateral circulation and polycythemia.

The net results of these mechanisms of adjustment and acclimatization are postulated in the triangles (7a)

and (7b). Visitors have a relatively lower oxygen supply and higher oxygen demand than residents.

Since factors which increase oxygen demand or decrease oxygen supply exacerbate myocardial ischemia and/or infarction the solid arrow (8a) indicates a deleterious effect. The broken arrow (8b) indicates that the higher oxygen supply and lower oxygen demand that residents have in comparison to visitors do not have deleterious effects on ischemia and/or infarction.

Problem Statement and Purpose

Is there a relationship between the severity of myocardial ischemia and/or infarction and the altitude of residence of patients hospitalized in a moderate altitude hospital?

Altitude exposure results in physiologic changes which differ between visitors and residents of altitude. The purpose of this study is to quantify, describe and compare characteristics and the hospital courses of visitors and residents of a moderate altitude environment hospitalized in an Intensive Care-Coronary Care Unit with the diagnoses of myocardial ischemia and/or infarction. The intent is to determine whether visitors have more severe complications from their ischemia and/or infarction. This will increase data concerning the course of this illness at moderate altitude.

CHAPTER II

REVIEW OF LITERATURE

An understanding of coronary artery disease, myocardial ischemia and infarction and the importance of an adequate oxygen supply and demand balance is essential. The extensive literature in these areas will be reviewed and summarized.

An understanding of man's response to altitude exposure is also important. Little is known concerning the effects of moderate altitude on patients with myocardial ischemia and/or infarction as studies have not been done in this specific area. However, extensive research has been done in the general area of altitude exposure, both acute and chronic. A thorough review of this literature is necessary to understand man's response to altitude in order to postulate specific modifications which could occur in response to moderate altitudes.

Literature concerning altitude exposure is extensive, contradictory and involves both human and animal subjects. This review will discuss these contradictions

and summarize those findings which are strongly supported by research. Only research involving human subjects will be reviewed unless specifically noted in order to avoid misconceptions based on data which may not be applicable to man.

Coronary Artery Disease

Coronary artery disease results from the deposition of atherosclerotic plaques within the coronary arteries which narrow their lumens reducing blood flow and oxygen delivery to the myocardium (Braunwald et al., 1980; Guyton, 1981; Hurst & Logue, 1974). If blood flow and/or oxygen delivery decrease below levels necessary to meet myocardial needs ischemic injury develops. If ischemic injury is prolonged myocardial infarction occurs (Alpert & Braunwald, 1980; Finch & Lenfant, 1972). Braunwald et al. (1980) define ischemia as "the condition of oxygen deprivation accompanied by inadequate removal of metabolites consequent to reduced perfusion" (p. 1279). The key concepts of a) "oxygen deprivation" which refers to cellular hypoxia, b) myocardial blood flow, and c) myocardial ischemia and infarction will be discussed to increase an understanding of coronary artery disease.

Cellular Hypoxia

Cellular hypoxia, a decreased supply of oxygen to

cells in relation to needs, results in the myocardium when the balance between myocardial oxygen supply and demand becomes inadequate (Comroe, 1974). This can occur in coronary artery disease where decreased flow reduces the amount of oxygen transported to cells. Any imbalance is extremely detrimental to the myocardium as normal function is impaired.

The susceptibility of the myocardium to cellular hypoxia results from its functional requirement to maintain constant tension for rhythmic contraction (Balke, 1964; Heath et al., 1977; Hurst et al., 1974). Myocardium consists of a complex system containing high concentrations of myoglobin and mitochondria which is primarly aerobic (Braunwald et al., 1980; Heath et al., 1977). Consequently, all cellular functions depend on adequate oxygen supplies for chemical reactions involving oxidative phosphorylation to provide energy (Holloway, 1979).

The role of oxygen in supplying energy through the formation of high energy phosphate bonds involves the Krebs cycle. With adequate oxygen both fatty acids, a preferential myocardial energy source, and either glucose or glycogen are converted to acetyl coenzyme A (Health et al., 1977) Acetyl coenzyme A enters the Krebs cycle and is converted to carbon dioxide and

hydrogen ions. Oxygen is required at this point for oxidative phosphorylation in which large amounts of energy are released and again stored in high energy phosphate bonds in the form of ATP (Holloway, 1979).

Cellular hypoxia, to which the heart with its minimal oxygen stores is susceptible, has severely detrimental effects on myocardial function as adequate energy from ATP is unavailable (Braunwald et al., 1980; Hurst et al., 1974). The energy deficits may result from decreased energy production or from insufficient formation of high energy bonds in ATP resulting in energy lost as heat rather than stored for future use (Braunwald et al., 1980; Holloway, 1979). This dysfunction both affects and is affected by coronary artery blood flow.

Coronary Artery Blood Flow

Coronary blood flow is regulated primarily by the oxygen needs of the myocardium (Coffman & Greg, 1961; Finch et al., 1972; Guyton, 1981). Coronary arteries are perfused by flow through the sinuses of Valsalva and coronary ostia during diastole when oxygen is delivered and metabolic waste products removed (Braunwald et al., 1980). Major coronary vessels branch to form a dense capillary network through which flow is controlled by

vasomotor tone and precapillary sphincters. The normal vascular bed has the reserve capability to increase flow by relaxation of precapillary sphincters and vasodilation resulting in an 80% increase in vessel lumens and a decreased resistance of 20% to 25% of basal levels. Coronary artery disease may limit flow at rest as well as limit this reserve capability due to atherosclerotic narrowing of vessels.

The reduced flow of coronary artery disease results in both a decreased oxygen delivery to myocardium and a decreased removal of metabolic waste products from cells. Both have a vasodilatory effect on coronary arteries although the exact mechanisms controlling this have not been conclusively determined (Braunwald et al., 1980; Guyton, 1981; Hurst et al., 1974).

The literature (Braunwald et al., 1980; Duling, 1972; Guyton, 1981) suggests that both a release of vasodilator substances and a relaxation of precapillary spincters results from hypoxia. The primary vasodilator substance released is adenosine. When hypoxia reduces the resynthesis of ATP by oxidative phosphorylation adenosine concentrations in the myocardium rise. Other vasodilator substances released in response to hypoxia which may increase flow include potassium, bradykinins, histamines and prostaglandins (Braunwald et al., 1980;

Needleman, Marshall, & Sobel, 1975). The relaxation of precapillary sphincters is postulated to result from the unavailability of adequate energy for maintenance of arteriolar muscle wall constriction (Guyton, 1981; Hurst et al., 1974).

Vasodilation and relaxation of coronary arteries also results from the toxic, depressant effects of metabolic waste products which are poorly removed when coronary artery disease decreases flow (Sobel, 1980). The toxic effects of these waste products which include hydrogen ions, lactate and carbon dioxide suppress the ability of cells to remain constricted and can increase blood flow.

Another important mechanism which attempts to compensate for hypoxia and decreased flow from coronary artery disease is the development of collateral coronary circulation. Investigators (Braunwald et al., 1980; Hurst et al., 1974; Lenfant et al., 1972) differ on whether collateral vessels are present at birth or new vessels develop in the presence of coronary artery disease. In either case flow through collateral vessels may contribute appreciably to meeting resting myocardial needs. Alpert et al. (1980) reports that in persons with coronary artery disease there is significantly better left ventricular function in regions supplied by col-

laterals than in regions without collaterals. Also with collaterals there is less risk of congestive heart failure and cardiomegaly with coronary artery disease.

The reserve capability of the coronary vasculature to increase flow to meet increased oxygen demands is limited by coronary artery disease. Numerous studies (Cohn & Braunwald, 1980) have demonstrated that there is impaired regional blood flow in myocardium supplied by obstructed coronary arteries. These studies indicate that when oxygen needs increase the augmentation of flow to the myocardium in persons with coronary artery disease is subnormal. This is probably due to the concept that coronaries distal to an obstruction are partially dilated to increase flow at a basal state. When oxygen needs increase the reserve capability for vasodilation is less.

Myocardial Ischemia and Infarction

Myocardial ischemia and/or infarction occur when hypoxia and decreased perfusion reach a critical level where oxygen supply to the myocardium is inadequate for oxygen demand. The primary results of ischemia and/or infarction include alterations in left ventricular function, alterations in cellular physiology and changes in myocardial metabolism (Barry, Brooker, Alderman &

Harrison, 1974; Braunwald et al., 1980; Mathey, Bleifeld & Franken, 1974). Impairment of left ventricular function results from depressed contractility and incomplete myocardial relaxation. Depressed contractility results from an interference in the normal role of calcium in contraction and possibly from decreased stores of ATP. This decreased contractility plus an increased resistance to filling due to incomplete myocardial relaxation leads to elevated ventricular filling pressures which increase the oxygen requirements of myocardium (Parker, 1972). Since ischemia is already present this results in increased left ventricular dysfunction.

If sufficient amounts of myocardium become ischemic left ventricular pump failure occurs (Alpert et al., 1980). Stroke volume and cardiac output fall below adequate levels and cardiogenic shock occurs. Survival and the degree of recovery following infarction are directly related to the extent of left ventricular dysfunction.

Conclusive evidence is limited concerning the effects of ischemia on the electrophysiology of the human heart (Braunwald et al., 1980). Research suggests that ischemia results in depressed action potentials, slow conduction and susceptibility to reentrant rhythms (El-Sherif & Lazzara, 1979). Abnormal electrophysiology can result in decreased coronary blood flow, increased

oxygen consumption and further compromise left ventricular function.

Alterations of myocardial metabolism induced by ischemia effect numerous biochemical pathways (Braunwald et al., 1980; Holloway, 1979). The effect on oxidative phosphorylation was discussed in the previous section, Cellular Hypoxia. Other metabolic pathways depressed by ischemia include carbohydrate, protein, fatty acid and calcium metabolism. Without adequate cellular metabolism, left ventricular function is further impaired.

Oxygen Supply and Demand in Relation to Myocardial Ischemia and Infarction

The severity of tissue damage in myocardial ischemia and/or infarction is increased by any factor which increases myocardial oxygen requirements or decreases supplies (Braunwald et al., 1974; Sobel et al., 1973). Factors which decrease hypoxia and increase blood flow may protect ischemic myocardium, reduce extension of an infarction and reduce early reinfarction due to an improved balance between oxygen supply and demand (Sobel et al., 1980). The importance of preserving ischemic myocardium is that complications such as arrhythmias, congestive heart failure, cardiogenic shock, extension of the infarction, pericarditis, thromboemboli

and death tend to increase as the amount of ischemia and necrotic myocardium increases (Holloway, 1979; Sobel et al., 1972; Sobel et al., 1980). The increased severity of myocardial ischemia and/or infarction reflected by increased complications results in poorer prognosis of recovery.

In the majority of patients hospitalized with ischemia or infarction there is a delay of several hours between onset of the ischemic event and medical intervention to improve the balance between oxygen supply and demand (Braunwald et al., 1980). Consequently, a patient's ability to improve his oxygen supply and demand balance both before and after hospitalization may improve his prognosis with myocardial ischemia and/or infarction.

Altitude Hypoxia

Exposure to altitude above sea level decreases the partial pressure of oxygen (pO_2) in ambient air. Although the percentage of atmospheric oxygen remains constant at 21% for all altitudes, a reduced barometric pressure results in expansion of compressible atmospheric gases (Heath et al., 1977). Since the number of gas molecules per unit volume of air decreases with expansion, less oxygen is inspired with normal respirations.

Altitude hypoxia results from this decreased pO_2

as movement of oxygen from atmosphere to tissue depends on a pressure gradient. When the pO_2 of ambient air decreases, both alveolar and arterial pO_2 will fall (Balke, 1964; Hartley, 1971; Lenfant et al., 1972; Pugh, 1965; Saltin, Grover, & Blomquist, 1968). The physiologic changes which occur when men travel or reside at altitude result primarily from this hypoxia.

Ambient, alveolar and arterial pO_2 fall steadily from sea level in proportion to the decreasing barometric pressure. Consequently, there is no distinct altitude of clinical significance. There is great variation among individuals in response to the hypoxia of altitude on their state of health and illness, genetic predispositions and other unknown factors and no one threshold altitude for the development of hypoxic symptoms exists (Balke, 1964; Heath et al, 1977; Houston, 1980). Reeves, Jokl and Cohn (1965) and Pugh (1965) report hypoxic effects of altitudes as low as 1,616 m and 2,287 m respectively in runners' performance times. Several other investigators (Grover, 1978; Hartley, 1971; Pugh, Gill & Lahiris, 1964; Pugh, 1965; Saltin et al., 1968) identify 1,982 m as the lowest altitude where cardiopulmonary changes are seen in healthy adults with hypoxic changes increasing with altitude. More consistent and measurable responses to altitude hypoxia begin around 3,100 m

with the majority of individuals above 4,200 m exhibiting signs of hypoxia (Heath et al., 1977; Houston, 1980; Reeves, Grover & Cohn, 1967; Sime, Penaloza, Ruiz, Gonzales, Covarrubias & Postigo, 1974). Based upon these findings a logical classification of altitudes within which general clinical signs of hypoxia can be grouped would include a) low altitude: below 1,600 m, b) moderate altitude: between 1,600 m and 3,100 m, and c) high altitude: above 3,100 m.

Only two studies (Graham & Houston, 1978; Marbarger, Wechsberg, Pestel, Vawter & Franzblau, 1953) could be found which examine the response of persons with cardiopulmonary disease and oxygen lack at sea level when exposed to the hypoxia of altitude. Graham et al. (1978) suggest that partial adaptation to acute exposure to altitude may result from living with variable levels of hypoxemia at sea level. Marbarger et al. (1953) exposed angina pectoris patients to simulated altitudes for such short periods (10 to 20 minutes) that results are inconclusive. However, these studies suggest the importance of individuals' states of health or illness in their response to the hypoxia of altitude.

Adjustments and Acclimatization

Physiologic changes are initiated by the lack of

oxygen at altitude. Immediate, short term responses which occur in the visitor to altitude are termed adjustments (Houston, 1980). Physiologic changes which occur over months and years in residents living at altitude are termed acclimatization. Acclimatization does not imply that all physiologic activity is restored to sea level values.

No specific time period differentiates adjustment and acclimatization as these processes overlap. However, most of the literature (Heath et al., 1977; Houston, 1980; Lenfant et al., 1971) implies that acute responses to altitude exposure continue for up to four weeks depending upon the magnitude of altitude and individual characteristics of subjects. The literature also discusses acclimatization in subjects who have been at altitude for at least six months although optimal acclimatization probably does not occur until much later.

The physiologic changes which occur in adjustments and acclimatization involve several mechanisms which attempt to minimize the detrimental effects of chronic hypoxia. These will be discussed below.

Hyperventilation

Hyperventilation occurs rapidly on acute exposure to altitude during activity, rest or sleep (Forster, Dempsey, Birnbaum, Reddan, Thoden, Grover & Rankin, 1969; Graham

et al., 1978; Houston, 1980; Lenfant et al., 1972; Reite, Jackson, Cahoon & Weil, 1975; Saltin et al., 1968). This increased alveolar pO_2 promotes oxygen transport by increasing the pressure gradient between alveoli and cells. Acutely, altitude hypoxia stimulates peripheral chemoreceptors which initiate responses from medullary respiratory centers (Comroe, 1974). Hyperventilation begins within hours of arrival at altitude but does not peak for several days (Lenfant et al., 1971; Severinghaus, Mitchell, Richardson, & Singer, 1963). This peak results from a slow readjustment of hydrogen ion concentration in cerebral spinal fluid which stimulates hyperventilation during a visitor's stay at altitude.

Ventilation increases in visitors have been noted at several moderate altitudes but consistent increases occur at 3,100 m (Lenfant et al., 1971). The magnitude of hyperventilation increases as the visitor ascends to higher altitudes with the development of a respiratory alkalosis (Graham et al., 1978; Heath et al., 1977; Hurtardo, 1964). Both respiratory rate and tidal volume increase although tidal volume increases more significantly (Heath et al., 1977).

Altitude residents maintain higher respiratory rates than sea level residents especially with activity (Heath et al., 1977; Houston, 1981; Lenfant et al.,

1971). However, acclimatization decreases this hyperventilation in comparison to altitude visitors and a concomitant correction of a respiratory alkalosis occurs (Heath et al., 1977; Hurtardo, 1964). It appears that a change in sensitivity to arterial pO_2 and pCO_2 results in residents' continued hyperventilation which is lower than that of visitors (Cummings & Semple, 1973; Lenfant et al., 1971).

Pulmonary Diffusion

A reduction in alveolar pO_2 limits pulmonary diffusion capacity unless compensatory mechanisms such as increased pulmonary diffusion occur (Lenfant et al., 1971). This mechanism has not been found in altitude visitors (DeGraff, Grover, Johnson, 1970; Heath et al., 1977; Houston, 1981; Hultgren & Grover, 1968; Lenfant et al., 1971). Although hyperventilation attempts to compensate for a decreased alveolar pO_2 several researchers (Lenfant et al., 1971; Reeves et al., 1967; West, 1962) suggest that this lack of increase in pulmonary diffusion capacity when exposed to the hypoxia of altitude results in a decreased oxygen uptake in visitors.

Oxygen uptake is decreased in altitude visitors both at rest and activity and probably contributes significantly to changes exhibited by visitors (Faulkner,

Kollias, Favour, Buskirk & Balke, 1968; Hansen & Evans, 1970; Hartley, 1971; Pugh, 1964; Reeves et al., 1967; Sime et al., 1974). Reeves et al. (1967) reports a decreased oxygen uptake at altitudes as low as 1,616 m. This decreased uptake compromises normal cellular functioning.

In contrast to visitors, altitude residents have increased pulmonary diffusing capacities (DeGraff et al., 1970; Houston, 1981; Hultgren et al., 1968). Lenfant et al. (1971) suggest that this may be due to changes in both the alveolar membrane's diffusing characteristics and the capillary blood volume. Mechanisms responsible for these changes include increased functional capillary surface area, redistribution of pulmonary flow, increased total blood volume, polycythemia and increased pulmonary artery pressures (Grover, Vogel, Voigt & Blount, 1966; Hartley, Alexander, Modelski & Grover, 1967; Lenfant et al., 1971).

The acclimatized resident appears to have a greater oxygen uptake than the visitor due to the above mentioned mechanisms although uptake, especially on exercise, may be only 75% to 80% of sea level norms (Heath et al., 1977; Houston, 1981). An increase in the oxygen uptake of residents occurs more rapidly at moderate than high altitudes and takes several months to develop.

Heart Rate

Heart rate increases in altitude visitors in response to hypoxic stimulation of the central nervous system which increases sympathetic activity (Cunningham, Becker, Kreuzer, 1965; Hultgren et al., 1968; Lenfant et al., 1971). Whether this increase occurs at rest as well as with activity is controversial. Several investigators (Balke, 1964; Hultgren et al., 1968; Jackson & Davies, 1960; Vogel & Harris, 1967) report an increase in resting heart rate proportional to the severity of decreased barometric pressure which continues during acute exposure. However, Pugh et al. (1964, 1965) and Heath et al., (1977) report no significant increase in resting heart rates during visitors' acute exposure to altitudes ranging from 2,500 m to 4,330 m. Reite et al. (1974) found a significant increase in heart rate during sleep in visitors to 4,300 m.

Following acclimatization, both resting and exercising heart rates tend to return to levels similar to or slightly above sea level norms (Balke, 1964; Houston, 1980). This decrease may be due to increased activity of compensatory mechanisms of acclimatization which increase oxygenation with a resulting decrease in sympathetic stimulation.

Cardiac Output

Cardiac output falls after as little as 24 hour exposure to altitude although a transitory initial rise due to increased heart rate has been noted by some investigators (Alexander, Hartley, Modelshi, & Grover, 1967; Hartley et al., 1967; Klausen, 1966; Lenfant, Torrance, Reynafarje, 1971; Reeves et al., 1967; Saltin et al., 1968; Sime et al., 1974; Vogel et al., 1967). Both resting and maximal stroke volume, a component of cardiac output, is initially unchanged but falls progressively during acute exposure (Grover et al., 1967; Pugh et al., 1964; Saltin et al., 1968). Reeves et al. (1967) and Klausen (1966) report decreased stroke volumes at altitudes as low as 3,110 m and 3,659 m respectively. Sime et al. (1974) found a decreased cardiac index in visitors at rest at the moderate altitude of 2,370 m.

A decreased resting and exercising stroke volume due to the depressant effect of hypoxia on myocardium probably overrides the initial sympathetic stimulation and results in a decreased cardiac output in visitors (Alexander et al., 1967; Hartley, 1971; Lenfant et al., 1971). Hartely (1971) suggests that hypoxic myocardium results in decreased contractility or compliance and Lenfant et al. (1971) suggest that weakening of myofilaments explains this decreased stroke volume and cardiac

output. Alexander et al. (1967) reports that the decreased plasma and blood volumes noted in visitors are not primary causes of decreased cardiac output.

Definitive literature is limited concerning cardiac output in acclimatized altitude residents. Balke (1967) and Houston (1980) state that cardiac output returns to sea level values following acclimatization both at rest and exercise. Other investigators (Alexander et al., 1967; Hartley et al., 1967; Hultgren et al., 1968; Lenfant et al., 1971) suggest that cardiac output remains below sea level values both at rest and activity from the myocardial depressant effect of chronic hypoxia. In comparison to visitors, residents tend to have higher cardiac outputs due to mechanisms of acclimatization.

Coronary Circulation

Extraction of oxygen from coronary blood is almost optimal at rest leaving little reserve to compensate for a decrease in arterial pO_2 or blood flow (Braunwald et al., 1980; Guyton, 1981). Acute myocardial hypoxia with a decreased pO_2 normally results in vasodilation and an increase in coronary blood flow (Grover, 1978; Heath et al., 1977). Few studies concerning either visitors or residents conclusively support or deny this response at altitude. Hultgren et al. (1968) and Houston (1980) suggest that an increase in coronary blood flow does

increase with acute exposure to altitude based on their own work and on a review of the literature. However, Grover et al. (1971) report a decreased coronary blood flow in the three subjects in comparison to flow at sea level both at rest and exercise ten days after exposure to 3,100 m. Arias-Stella and Recavarren (1962) suggest that coronary blood flow may be increased in residents as a result of an increase in the diameter of the right coronary artery following right ventricular hypertrophy. More data is necessary before the importance of this mechanism in adjustment and/or acclimatization can be predicted.

The limited research on coronary vasodilation at altitude makes it useful to review the response of a widely studied circulatory bed, the retinal vasculature, for possible analogies. A normal response of the retinal vasculature exposed to altitude includes engorgement and tortuosity (McFadden, Houston, Sutton, Powles, Gray, & Roberts, 1981). These changes may be accompanied by increased capillary membrane permeability and capillary rupture or leakage resulting in retinal hemorrhage (Frayser, Gray, & Houston, 1974; Wilson, 1973). If similar changes occur in coronary vessels both acute and chronic problems in oxygen transport may be traced to these changes.

Collateral Coronary Circulation

An essential mechanism involving coronary circulation which improves oxygen diffusion to tissue is increased vascularization of the myocardium (Arias-Stella & Topilsky, 1971; Heath et al., 1977; Houston, 1980; Hultgren et al., 1967; Moret, Covarrubias & Coudert, 1972). This collateral coronary vascularization increases in altitude residents in response to chronic altitude hypoxia. Voors and Johnson (1971) suggest that a suspected decreased cardiovascular disease mortality at high altitude may be due to this increased collateral circulation. Collateral circulation may develop through recruitment of existing but nonperfused collateral vessels or through formation of new vessels (Houston, 1980). It is probable that collaterals make an important contribution to acclimatization to altitude. Increased vascularization shortens the distance between capillaries and tissue and increases the amount of functional capillary surface area for oxygen diffusion (Comroe, 1974). Both of these improve oxygen transport by increasing myocardial perfusion.

Polycythemia

Polycythemia, an increase in erythrocytes and hemoglobin takes months to years to fully develop in the

acclimatized altitude resident (Houston, 1980; Pugh et al., 1964). It is an extremely important mechanism for a compensation of the decreased pO_2 at altitude as polycythemia increases the oxygen carrying capacity of blood (Comroe, 1974; Hartley, 1971; Hultgren et al., 1968; Lenfant et al., 1971; Moret et al., 1972). Erythropoietic stimulation is elicited by hypoxia and is directly proportional to it. Consequently, hemoglobin increases directly with altitude of residency developing more slowly at moderate altitudes than high altitudes. Finch et al. (1972) identify polycythemia as a mechanism of acclimatization rather than adjustment to altitude as the process is too slow to be of importance to the altitude visitor.

The potential problem of increased blood viscosity resulting from polycythemia has been considered as hemoglobin may increase 30% to 50% from sea level values (Houston, 1980). Banchero, Sime, Penaloza, Cruz, Gamboa, & Marticorena (1966) and Hultgren et al. (1968) report that polycythemia of altitude does not reduce blood flow nor is it associated with increased coronary artery thrombosis.

2, 3-DPG

2, 3-DPG is an intermediary product of glycolosis which decreases hemoglobin's affinity for oxygen and,

therefore, increases the oxygen available for diffusion at the cellular level (MacDonald, 1977).

The role of 2, 3-DPG in adjustments and acclimatization to altitude which was once thought to be an important mechanism is now being questioned (Heath et al., 1977; Lenfant et al., 1971; Morpurgo, Battaglia, Carter, Modiano, & Passi, 1972). Without further data the effect of 2, 3-DPG in both adjustments and acclimatization cannot be postulated.

Tissue Diffusion of Oxygen

Mechanisms of adjustment discussed above are ultimately for the purpose of increasing diffusion of oxygen to cells. However, Lenfant et al. (1971) suggest that since mixed venous pO_2 falls below sea level values in proportion to altitude neither the ventilatory or circulatory mechanisms discussed are adequate to completely compensate for the hypoxia of altitude. It is postulated that numerous unidentified changes occur in tissues to improve diffusion and utilization of oxygen but it is unknown what role this has in the adjustment of visitors of altitude.

The effects of chronic exposure to altitude on this final step of oxygen transport is unknown. Tissue diffusion involves movement of oxygen from blood to cells

and within cells to mitochondria. Physical diffusion is the basic process of oxygen movement and the rate depends on several variables (Braunwald et al., 1980; Lenfant et al., 1971). These include a) the oxygen pressure gradient between capillary blood and mitochondria, b) the proximity of capillaries to cells and c) the inherent properties of cells which affect diffusion.

The mechanisms of acclimatization discussed above improve tissue oxygenation by their effect on these first two variables. Lenfant et al. (1971) state that acclimatization results in numerous unknown changes in the third variable which improves tissue diffusion and oxygen utilization. These changes may include increased numbers of mitochondria and increased myoglobin which increase oxygen diffusion rate, both of which have been found with acclimatization of animals (Heath et al., 1977; Houston, 1980; Lenfant et al., 1971).

Summary

The decreased pO_2 at altitude initiates physiologic changes. These changes differ between visitors and residents of altitude as depicted in the Conceptual Model (Figure 1). Visitors experience relatively greater hyperventilation, higher heart rates and lower plumonary diffusion, cardiac output, coronary collateral circulation, polycythemia and tissue diffusion when compared

with residents. Since the adjustments demonstrated by visitors may increase myocardial oxygen requirement and decrease oxygen supply as compared with residents, visitors with coronary artery disease may be susceptible to more severe myocardial ischemia and infarction.

Research Questions

The specific research questions of this study are:

1. Do visitors to moderate altitudes, hospitalized with myocardial ischemia and/or infarction, have more complications than residents with myocardial ischemia and/or infarction?

2. Do visitors to moderate altitudes, hospitalized with myocardial ischemia and/or infarction, have a longer hospitalization than residents with myocardial ischemia and/or infarction?

3. Do visitors to moderate altitudes, hospitalized with myocardial ischemia and/or infarction, require a longer usage period of supplemental oxygen?

Answers to these questions may increase knowledge concerning whether there is a relationship between the severity of myocardial ischemia and/or infarction and the altitude of residence of patients hospitalized in a moderate altitude hospital.

CHAPTER III

METHODOLOGY

Design

The design of this study was ex-post facto, descriptive. Charts were reviewed for data concerning signs and symptoms in patients with myocardial ischemia and/or infarction. This design was chosen because of the lack of prior research in this problem area. It allowed description of the relationship among several variables and provided insight into areas for further research. Also, the small patient population in the moderate altitude hospital used for the study necessitated examining data over a long period of time to increase the sample size.

Setting

The study was conducted in a 64 bed county hospital with a five bed intensive care coronary care unit located at an elevation of approximately 1,900 m. The hospital serves a geographical area with primarily moderate altitudes of 1,829 m to 3,100 m. The resident population served contained approximately

12,000 people and was the primary hospital serving visitors in two national parks, two wilderness areas, three national forest and two ski resorts.

Sample

All subjects with primary diagnoses of myocardial ischemia or myocardial infarction admitted to the Intensive Care-Coronary Care Unit between October 1, 1978 and September 30, 1981 inclusively were used as subjects in this retrospective study with the following exclusions:

1. Subjects admitted following trauma or accident.

2. Subjects who were visitors but who normally resided at altitudes equal to or greater than 1,600 m.

3. Subjects who had lived as residents for less than six months or had been visitors for more than four weeks.

This 36 month study period was chosen to minimize any effect of seasonal change on subjects as well as to maximize the size of the sample.

The researcher identified subjects with diagnoses of myocardial ischemia or infarction by reviewing monthly computerized patient census sheets coded for diagnoses. The researcher then reviewed the medical record of each identified subject and assigned him to the visi-

tor group or the resident group according to his place of residence. Each group was subdivided into subjects with myocardial ischemia and subjects with myocardial infarction.

Operational Definitions

Moderate Altitude

Moderate altitude is defined as any geographical altitude between 1,600 m and 3,100 m according to United States Geological Survey records.

Visitor

Visitor is defined as a person who resided at an altitude below 1,600 m and had spent less than four weeks at or above 1,600 m preceding his hospitalization. Residence was established by demographic information, medical history, and nursing history in the medical record.

Resident

Resident is defined as a person who had resided in the area served by the study hospital for not less than six months prior to his hospitalization. Residence was established by demographic information, medical history, and nursing history in the medical record.

Myocardial Ischemia

Myocardial ischemia is defined as a condition of

oxygen deprivation and decreased perfusion of the myocardium documented in the medical record by a) History, and b) Electrocardiogram changes compatible with tissue ischemia including peaked or inverted T waves.

Myocardial Infarction

Myocardial infarction (Refers to acute myocardial infarction in this study) is defined as a condition of injured or necrosed myocardium documented in the medical record by two of the following conditions: a) History, and b) Elevated cardiac enzymes (CPK and LDH), and/or c) Electrocardiogram changes compatible with tissue death i.e., the presence of Q waves or EKG changes compatible with injured or necrosed myocardium including ST segment or T wave changes in conjunction with elevated cardiac enzymes.

Complications

Complications refers to the following conditions as recorded in the medical record:

1. Arrhythmias: Any cardiac rhythm which is not a regular sinus rhythm or a sinus rhythm with a rate less than 60 or greater than 100 beats per minute. Arrhythmia Days were the number of days on which an arrhythmia was documented regardless of number of occurrences each day.

2. Congestive heart failure: The presence of

dyspnea, orthopnea, cough, rales, wheezes and/or pink, frothy sputum.

3. Cardiogenic shock: The presence of a systolic blood pressure below 70 mmHg with confusion or other signs of diminished cerebral perfusion, pale, cool, clammy skin, a urinary output below 30 ml per hour and/or metabolic acidosis.

4. Extension of infarction: A recurrence of the events defined above for myocardial infarction.

5. Pericarditis: The presence of a pericardial friction rub, chest pain increased with deep breathing, and/or ST elevation in all EKG leads without reciprocal depression in opposite leads and without significant Q waves.

6. Thromboemboli: The presence of hypoxia, right ventricular failure with atrial arrhythmias, and distended neck veins, decreased cardiac output with hypotension, tachycardia and confusion, and/or sudden onset of chest pain.

7. Death: The death of the patient during his hospitalization.

Data Collection Procedure

According to the operational definitions medical records were coded with an identification number and divided into two main groups; visitors and residents.

Each main group was divided into two diagnoses subgroups of myocardial ischemia and myocardial infarction. All parts of a subject's medical record were used for information. A data collection sheet (Appendix) was used to record pertinent data during each chart review.

Human Subjects Considerations

Each subject's chart was assigned an identification number. One master sheet listing each subject's name and identification number was made and kept by the investigator for further information retrieval only. At the conclusion of the study the list was destroyed. Data was analyzed using this identification number and at no time was a subject's name used in any report of the study or study results. Due to the retrospective nature of the study informed consent was not obtained but confidentiality was maintained as described above. The only risk to subjects was invasion of privacy and privacy was protected as described above. The potential benefit to improvement in the delivery of health care to the public through increased knowledge concerning altitude effects outweighed this invasion of privacy.

CHAPTER IV

RESULTS

Data was analyzed using different statistical tests. A frequency distribution of total visitors and residents was tabulated for descriptive information. An independent student T-test was performed to determine significant differences between visitors and residents with myocardial ischemia and with infarction. To determine significant relationships between visitor and resident groups and complication variables a chi-square was used as a measure of association. A non-parametric Spearman Rho correlation was used to measure the strength and direction of relationships between altitude of residence and other variables. The level of statistical significance in this study was .05.

Biographical Data

A total of 112 subjects with diagnoses of myocardial ischemia or infarction were identified within the 36 month study period. Table 1 presents a summary of subjects' biographical data. Forty-eight subjects (41%) were visitors while 66 subjects (59%) were residents.

Table 1

Descriptive Characteristics Obtained by a Frequency Distribution of Total Visitors and Residents, Visitors and Residents with Myocardial Ischemia and Visitors and Residents with Myocardial Infarction

Demographic Variables	Total Subjects				Subjects with Ischemia				Subjects with Infarction			
	Visitors (n=46)		Residents (n=66)		Visitors (n=25)		Residents (n=46)		Visitors (n=21)		Residents (n=20)	
	n	%	n	%	n	%	n	%	n	%	n	%
Sex												
Males	36	78.3	49	74.2	19	76.0	33	71.7	17	81.0	16	80.0
Females	10	21.7	17	25.8	6	24.0	13	28.3	13	28.3	4	20.0
Marital Status												
Married	36	78.3	48	72.7	22	88.0	35	76.1	14	66.7	13	65.0
Unmarried	10	21.7	18	27.3	3	12.0	11	23.9	7	33.3	7	35.0

Table 1 Continued

Demographic Variables	Total Subjects				Subjects with Ischemia				Subjects with Infarction			
	Visitors (n=46)		Residents (n=66)		Visitors (n=25)		Residents (n=46)		Visitors (n=21)		Residents (n=20)	
	n	%	n	%	n	%	n	%	n	%	n	%
Employment Status												
Employed	16	34.8	23	34.8	5	20.0	15	32.6	11	52.4	8	40.0
Retired	27	48.7	36	54.6	18	72.0	26	56.5	9	42.9	10	50.0
Unemployed	3	6.5	7	10.6	2	8.0	5	10.9	1	4.8	2	10.0
	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Age	61.8	39-77	64.4	37-83	65.2	51-77	64.5	37-83	57.8	39-74	64.0	50-82
Altitude of residence (meters)	364.4	1-1567	1928.8	1707-2192	379.5	1-1567	1910.2	1707-2056	346.4	3-1567	1971.6	1900-2192

The visitor group was equally divided between myocardial ischemia (54%) and infarction (46%) whereas the majority of residents were diagnosed with ischemia (70%).

A chi-square was used as a measure of association between ischemia and infarction groups. There were no significant associations. A non-parametric Spearman Rho correlation between altitude and diagnosis showed no significance.

Distribution of subjects according to age, sex, marital status, and employment was similar for visitors and residents with ischemia (Table 1). The infarction group, however, did differ. Visitors were younger and more likely to be employed than residents (Table 1).

Visitors in the study resided at altitudes ranging from 1 m to 1,568 m (Table 1). Residents lived at moderate altitudes ranging from 1,707 m to 2,192 m. Visitors with ischemia and visitors with infarction had similar mean altitudes of residence of 379.5 m and 346.4 m respectively. Residents with ischemia and with infarction also had similar mean residence altitudes of 1,910.2 m and 1,971.6 m respectively. Five potential subjects who were visitors to the study area were eliminated from the study as they resided at moderate altitudes ranging from 1,770 m to 2,225 m.

Seven subjects were air evacuated from the study

hospital to a larger hospital for either further evaluation or treatment unavailable at the study hospital. Four residents with ischemia, two residents with infarction, and one visitor with infarction were evacuated. Since the length of hospitalization was shortened for these subjects, results on some variables may have been affected (See Results).

Research Question One

> Do visitors to moderate altitudes hospitalized with myocardial ischemia or infarction have more complications than residents with myocardial ischemia or infarction?

An independent student T-test was performed to determine significant differences in arrhythmias (Table 2). A chi-square was used to measure associations between other complication variables (Table 3). There were no statistically significant differences or relationships in complication variables between visitors or residents with ischemia. Other than congestive heart failure few complications occurred in any ischemia subjects. The only statistically significant comparison between visitors and residents with infarction were with the arrhythmias of sinus bradycardia, sinus tachycardia and second degree A-V block, type I.

Arrhythmias

Sinus bradycardia was the most frequently occurring

Table 2

Mean Differences Obtained by an Independent Student T-Test in Numbers of Arrhythmia Days Between Visitors and Residents with Myocardial Ischemia and Between Visitors and Residents with Myocardial Infarction

Type of Arrhythmia	Subjects with Ischemia (n=71)						Subjects with Infarction (n=41)					
	Visitors			Residents			Visitors			Residents		
	n	Mean	S.D.	n	Mean	S.D.	n	Mean	S.D.	n	Mean	S.D.
Sinus bradycardia	12	1.16	1.5	26	1.33	1.6	11	2.57	4.3	9	.65[a]	.9
Sinus tachycardia	6	.40	.8	7	.70	2.3	4	.29	.6	12	1.90[b]	3.1
Atrial flutter	0	.00	.0	1	.07	.4	0	.00	.0	3	.20	.5
Atrial fibrillation	1	.08	.4	4	.09	.3	1	.09	.4	5	.95	2.8
Paroxysmal atrial fibrillation	3	.12	.3	1	.04	.3	2	.09	.3	1	.05	.2
Junctional rhythm	2	.32	1.4	4	.09	.3	5	.67	1.4	6	.75	1.5
Right bundle branch block	0	.00	.0	5	.46	1.5	0	.00	.0	1	.05	.2
Left bundle branch block	3	.40	1.2	6	.46	1.3	4	.43	1.1	3	.95	3.2
First degree A-V block	1	.04	.2	5	.46	1.4	1	.33	1.5	6	.85	1.5
Second degree A-V block Type I	0	.00	.0	1	.02	.1	1	.05	.2	6	.70[c]	1.3

Table 2 Continued

Type of Arrhythmia	Subjects with Ischemia						Subjects with Infarction					
	Visitors			Residents			Visitors			Residents		
	n	Mean	S.D.	n	Mean	S.D.	n	Mean	S.D.	n	Mean	S.D.
Second degree A-V block Type II	0	.00	.0	0	.00	.0	1	.10	.4	2	.10	.3
Third degree A-V block	0	.00	.0	0	.00	.0	2	.29	1.0	3	.40	1.1
Premature ventricular contraction	7	.60	1.1	12	.30	.6	13	1.29	2.0	14	1.10	1.1
Ventricular escape rhythm	0	.00	.0	0	.00	.0	1	.05	.2	2	.10	.3
Ventricular tachycardia	2	.08	.3	1	.02	.2	10	.57	.7	4	.35	.8
Ventricular fibrillation	0	.00	.0	0	.00	.0	2	.10	.3	2	.10	.3
Cardiac standstill	0	.00	.0	2	.04	.2	2	.10	.3	1	.05	.2

Note. n = Number of subjects diagnosed with arrhythmia and Mean = mean number of days arrhythmia occurred.
[a]significant value, p = .057; [b]significant value, p = .024; [c]significant value, p = .034; All other values were not significant.

Table 3

Comparisons Obtained by a Chi-Square Statistic in the Incidence of Nonarrhythmia Complications Between Visitors and Residents with Myocardial Ischemia and Between Visitors and Residents with Myocardial Infarction

Nonarrhythmia Complications	Subjects with Ischemia (n=71)					Subjects with Infarction (n=41)				
	Visitors		Residents		X^2	Visitors		Residents		X^2
	n	%	n	%		n	%	n	%	
Congestive heart failure	6	24.0	13	28.3	.01	9	42.9	6	30.0	.28
Cardiogenic shock	0	0.0	1	2.2	.00	0	0.0	1	5.0	.00
Extension of infarction	0	0.0	0	0.0	--	2	9.5	1	5.0	.00
Pericarditis	0	0.0	1	2.2	.00	2	9.5	5	25.0	.81
Thromboembolus	0	0.0	0	0.0	--	2	9.5	2	9.5	.00
Death	0	0.0	2	4.3	.09	2	9.5	0	0.0	.48

Note. No values were significant at the $p \leq .05$ level.

arrhythmia in all groups. Visitors with infarction had significantly greater numbers of sinus bradycardia days (mean 2.57, $p \leq .05$) than residents (mean .65). However, visitors with infarction had significantly fewer days of sinus tachycardia (mean .29, $p \leq .024$) and second degree A-V block, type I (mean .05, $\leq .034$) than residents (tachycardia mean 1.9 and 2° A-V block, type I mean .7) (Table 2).

Nonarrhythmia Complications

There were no significant relationships between either visitor or resident groups on the complication variables of congestive heart failure, cardiogenic shock, extension of infarction, pericarditis, thromboembolus, or death (Table 3).

Research Question Two

> Do visitors to moderate altitudes hospitalized with myocardial ischemia or infarction have longer hospitalizations than residents with myocardial ischemia or infarction?

An independent student T-test was used to determine significant differences on this variable (Table 4). Visitors with myocardial ischemia had shorter hospitalizations (mean 5.2 days) than residents with ischemia (mean 6 days). Similarly, visitors with myocardial infarction (mean 11.9 days) had shorter hospitalizations than residents with infarction (mean 13.7 days). However, neither

Table 4

Mean Differences Obtained by an Independent Student T-Test in Number of Days Hospitalized Between Visitors and Residents with Myocardial Ischemia and Between Visitors and Residents with Myocardial Infarction

Number Days Hospitalized	Subjects with Ischemia (n=71)						Subjects with Infarction (n=41)					
	Visitors			Residents			Visitors			Residents		
	n	Mean	S.D.	n	Mean	S.D.	n	Mean	S.D.	n	Mean	S.D.
Before omission of subjects who were air evacuated or died	25	5.2	2.8	46	6.0	3.6	20	11.9	6.8	21	13.7	4.9
After omission of subjects who were air evacuated or died	25	5.2	2.8	42	6.1	3.6	19	13.4	6.7	19	14.8	5.5

Note. No values were significant at the $p \leq .05$ level.

of these differences were statistically significant.

For 11 subjects, hospitalizations were shortened by either air evacuation or death. Consequently, these subjects were omitted and mean values for hospital days recalculated. Differences between ischemia groups and infarction groups were relatively unchanged (Table 4). Differences between visitors and residents with infarction decreased while the actual length of hospitalization increased slightly.

Research Question Three

> Do visitors to moderate altitudes hospitalized with myocardial ischemia or infarction require supplemental oxygen for a longer period of time?

To determine significant differences an independent student t-test was done (Table 5). Visitors with myocardial ischemia required supplemental oxygen for an average of only 2.9 days while residents with ischemia had a 3.3 day average use of oxygen. Similarly, visitors with infarction used supplemental oxygen for only 6.5 days. Residents with infarction required oxygen for an average of 8 days. Neither of these differences were statistically significant.

When patients who were air evacuated or who died were omitted, differences between ischemia groups and infarction groups remained non-significant (Table 5).

Table 5

Mean Differences Obtained by an Independent Student T-Test in Number of Days with Supplemental Oxygen Between Visitors and Residents with Myocardial Ischemia and Between Visitors and Residents with Myocardial Infarction

Number Days Supplemental Oxygen Usage	Subjects with Ischemia (n=71)						Subjects with Infarction (n=41)					
	Visitors			Residents			Visitors			Residents		
	n	Mean	S.D.	n	Mean	S.D.	n	Mean	S.D.	n	Mean	S.D.
Before omission of subjects who were air evacuated or died.	25	2.9	1.6	46	3.3	2.2	20	6.5	6.0	21	8.0	5.0
After omission of subjects who were air evacuated or died.	25	2.9	1.6	42	3.4	2.3	19	7.1	6.2	19	8.4	5.1

Note. No values were significant at the $p \leq .05$ level.

Supplemental oxygen usage by visitors with ischemia was unchanged while there was a slight increase by residents with ischemia. Differences between visitors and residents with infarction decreased while oxygen usage increased slightly.

Ancillary Results

Correlations

A non-parametric Spearman Rho correlation was performed to measure the strength and direction of relationships between altitude of residence and all other variables (Table 6). Eleven variables were significantly correlated with increasing altitude of residence. Atrial flutter and second degree A-V block, type I were positively correlated with altitude ($p \leq .01$). As altitude increased, the frequency of these arrhythmias also increased. Paroxysmal atrial tachycardia ($p \leq .025$) and ventricular tachycardia ($p \leq .031$) were negatively correlated with altitude. The occurrence of hypertensive episodes correlated positively with altitude ($p \leq .002$).

Admission blood pressure, both systolic ($p \leq .002$) and diastolic ($p \leq .001$), correlated negatively with altitude. There were no other significant correlations between physiologic admission parameters and altitude of residence.

Three variables concerning subjects' prior disease

Table 6

Significant Correlations Obtained from a Non-Parametric Spearman Rho Correlation Between Altitude of Residence and Other Variables

Variable	Altitude of Residence		
	n	rho	p*
Atrial flutter	4	+.20	.01
Paroxysmal Atrial Tachycardia	7	-.19	.025
Second Degree A-V block, Type I	8	+.20	.01
Ventricular Tachycardia	17	-.18	.031
Admission Systolic Blood Pressure	112	-.28	.002
Admission Diastolic Blood Pressure	112	-.37	.001
Family History Cardiac Disease	108	+.20	.021
History Previous Myocardial Infarction	112	+.17	.033
History Respiratory Disease	112	+.21	.014
Hypertensive Episode	112	+.26	.002
Oral Inotropic Med. Days	112	+.21	.013

Note. Significance level set at $p \leq .05$.

history correlated positively with altitude of residence. These included family history of cardiac disease ($p \leq .021$), history of previous myocardial infarction ($p \leq .033$), and history of respiratory disease ($p \leq .014$). No other subject history variables correlated significantly with altitude of residence.

Finally, there was a positive correlation between altitude of residence and oral inotropic medication days ($p \leq .013$).

Other Significant Variables

Significant differences were found between the admission systolic and diastolic blood pressure of both visitors and residents with ischemia and with infarction (Table 7). Visitors with myocardial ischemia had higher admission systolic blood pressures and diastolic blood pressures than residents with ischemia ($p \leq .001$). This same relationship was seen between visitors and residents with myocardial infarction. Visitors had higher systolic ($p \leq .05$) and diastolic blood pressures ($p \leq .014$) than residents with infarction.

Hemoglobin and Hematocrit - Unexpected Results

There were no significant differences in hemoglobin and hematocrit between visitors and residents with

Table 7

Mean Differences Obtained by an Independent Student T-Test in Systolic and Diastolic Blood Pressures Between Visitors and Residents with Myocardial Ischemia and Between Visitors and Residents with Myocardial Infarction

	Subjects with Ischemia (n=71)							Subjects with Infarction (n=41)						
	Visitors			Residents				Visitors			Residents			
	n	Mean	S.D.	n	Mean	S.D.	p*	n	Mean	S.D.	n	Mean	S.D.	p*
Admission Systolic Blood Pressure	25	158	32.0	46	134	24.1	.001	20	145	23.9	21	127	37.2	.05
Admission Diastolic Blood Pressure	25	94	13.0	46	83	17.5	.011	20	95	12.9	21	80	23.3	.014

* Significance set at $p \leq .05$.

ischemia or infarction. Visitors and residents with ischemia had similar mean hemoglobins (15.16 gms % and 14.87 gms % respectively) and similar mean hematocrits (42.99% and 43.04% respectively). Visitors and residents with infarction also had similar mean hemoglobins and hematocrits (mean hemoglobin of visitors 15.09 gms % and of residents 15.26 gms %; mean hematocrits 43.73% and 44.58% respectively).

CHAPTER V

DISCUSSION

Physiologic changes occur in both visitors and residents as their environmental altitude increases. These changes, primarily cardiopulmonary, are initiated by the decreased partial pressure of oxygen with increased altitude and differ between visitors and acclimatized residents. These physiologic differences may result in different responses to illness such as myocardial ischemia or infarction where severity of the illness is affected by myocardial oxygen supply.

Extensive literature exists concerning the effects of high altitude above 3,100 m on healthy men. However, little is known about how people with disease respond when exposed to the more commonly encountered moderate altitudes ranging from 1,600 m to 3,100 m. Consequently, more data is necessary to predict responses to illness at moderate altitude and to provide optimal health care.

This study compared visitors to a moderate altitude hospitalized with myocardial ischemia and/or infarction with hospitalized residents of that moderate altitude.

The purpose was to quantify, describe, and compare visitors' and residents' characteristics and their hospital courses. The intent was to determine if there was a relationship between severity of myocardial ischemia and/or infarction and altitude of residence.

Biographical Data

Disease group distribution within the visitor population and the resident population differed with 46% of all visitors diagnosed with infarction as compared to 30% of residents with infarction. Based on significant risk factors for infarction, visitors would be expected to have less infarction than residents as visitors were younger and had fewer previous myocardial infarctions. The important finding that a larger percentage of the visitor group had myocardial infarctions suggests that altitude does affect coronary artery disease. This strongly supports the Conceptual Model (Figure 1) which proposes that altitude detrimentally affects the ability of visitors to regulate the balance of oxygen supply and demand.

Although epidemiologic studies on the incidence of myocardial infarction vary depending on population and disease criteria, Silber and Katz (1975) state that the incidence of myocardial infarction is 20% of all ischemic heart disease. Visitors with coronary artery

disease demonstrated a much higher infarction rate and this further supports the proposed effects of altitude in Figure 1.

The Conceptual Model (Figure 1) suggests that visitors have a higher oxygen demand and lower tissue oxygen supply than residents due to hyperventilation, increased heart rate, and decreased pulmonary diffusion, cardiac output, collateral circulation and tissue diffusion. These factors can decrease myocardial blood flow and increase hypoxia of the visitor in comparison with the altitude resident. When superimposed on coronary artery disease which decreases the reserve capability of coronary vasculature to increase flow to meet increased oxygen demands, these altitude variables may increase the severity of an ischemic event in the visitor resulting in infarction. Although this Conceptual Model was developed from research at high altitudes, the visitor's higher rate of infarction supports the model even at moderate altitudes.

Another cause of disease group differences could have been visitors' unfamiliarity with the study hospital and local physicians. Unfamiliarity could lead to a delay from onset of the ischemic event to initiation of medical care either through the visitor's hesitancy to seek treatment at unknown facilities or through

difficulty in actually locating the hospital. Since the severity of myocardial injury can be modified by medical care which improves oxygen supply and demand balance, this delay could result in tissue infarction. A combination of this delay plus altitudes' detrimental effect on the balance of oxygen supply and demand could explain the higher rate of infarction in visitors.

Unfamiliarity with medical facilities also could have resulted in fewer ischemia visitors seeking medical care. Visitors with only mild symptoms which disappear without treatment, who on hospitalization would be diagnosed with ischemia, may avoid medical care from unknown physicians. The resident with an established patient-physician relationship may be less hesitant in reporting mild symptoms to his physician. This would effect the disease distribution between visitors and residents.

Finally, a patient self-selection process may account for the different disease distribution. Potential visitors with coronary artery disease manifested by previous myocardial infarction and susceptible to ischemia may avoid travel to moderate altitude due to fear of altitude induced symptoms. Absence of this group could have caused a selection bias in the visitor population.

If these potential visitors had traveled to moder-

ate altitude they may have experienced ischemia due to an inability of atherosclerotic coronary arteries to increase flow when altitude exposure disrupted oxygen supply and demand balance. Due to previous experience, this group could have been more likely to recognize symptoms of myocardial ischemia and seek medical care rapidly. This would have increased the percentage of visitors diagnosed with ischemia.

This potential group, however, could also have increased the percentage of visitors with infarction since previous infarctions increase the risk of reinfarction. The actual effect of visitor self-selection is difficult to assess but could have affected the distribution of disease groups.

Research Questions

Visitors hospitalized with myocardial ischemia did not have more complications than residents with ischemia. Based on a review of all complication variables, visitors hospitalized with myocardial infarction did not have more complications than residents with infarction.

Neither visitor group had longer hospitalizations than its corresponding resident group. Similarly, visitors with ischemia did not require longer usage periods of supplemental oxygen nor did visitors with infarction use supplemental oxygen longer than their corresponding

resident group. These findings suggest that the reduced pO_2 at moderate altitude is not critical enough to initiate adaptation and acclimitization processes affecting the hospital course of coronary artery disease patients. Although arterial pO_2 falls from a sea level value of 94 mmHg to 60 mmHg at moderate altitude, there is little change in the arterial oxygen saturation which remains above 90% (Comroe, 1974; Guyton, 1981). During hospitalization oxygen saturation may be high enough to minimize differences in oxygen supply and demand between visitors and residents.

Another possibility suggested by these results is that coronary artery disease may alter the physiologic responses to altitude. When ischemia and/or infarction occur the resulting pathologic changes may mask most effects of moderate altitude exposure during hospitalization. Impairment of left ventricular function, alterations in cellular physiology and changes in myocardial metabolism which occur with ischemia and infarction may be so stressful that any effect of moderate altitude on oxygen supply and demand is unimportant.

There were significant differences in the infarction group on a few arrhythmias usually classified as non-lifethreatening. Visitors had more sinus bradycardia but less sinus tachycardia or second degree A-V block

than residents. Since several factors influence these arrhythmias including the location of disease in the coronary arteries and location of an infarction, it is unclear whether these are affected by altitude.

Other Findings

The negative correlation between ventricular tachycardia and altitude of residence suggests better myocardial oxygenation in the resident group. Since ventricular tachycardia, a life threatening arrhythmia related to myocardial hypoxia, occurs less frequently as altitude of residence increases, acclimatization may have a beneficial effect on the balance between oxygen supply and demand when ischemia or infarction occur.

Admission blood pressure was higher in visitors and tended to increase as altitude of residence decreased. This reflects an increased sympathetic activity in the visitor possibly due to increased hypoxia when compared with the resident. Increased anxiety caused by unfamiliar medical facilities and personnel could also result in increased sympathetic activity in the visitor reflected in elevated blood pressures.

Regardless of the cause of the visitor's increased blood pressure on hospital admission, this could have contributed to the higher rate of infarction among visitors. An elevated blood pressure can increase afterload

causing a rise in oxygen consumption. If this increase exceeds oxygen delivery, a common problem in coronary artery disease, it may lead to extension of the area of ischemia and result in infarction.

The absence of statistically significant differences in hemoglobin and hematocrit was important as this was unexpected from the literature. Although hypoxia stimulates hemoglobin production in both visitors and residents, this mechanism takes months to fully develop and any increase would not be clinically measurable in visitors. All mean hemoglobins and hematocrits were within a normal range for both sea level and moderate altitude. Normal laboratory values for the moderate altitude study hospital ranged from 13.0 to 18.0 gms % hemoglobin and 40.0 to 55.0% hematocrit. These are higher than normal sea level values for hemoglobin, 11 to 17 gms % and for hematocrit, 37.0 to 54.0%.

Summary and Implications

The data is this study did not indicate a relationship between the severity of myocardial ischemia and/or infarction and the altitude of residence of subjects in a moderate altitude hospital after hospitalization. There were no differences between visitors and residents with myocardial ischemia or with infarction in complications during hospitalization, length of hospitalization,

or length of supplemental oxygen usage.

The findings, however, do suggest that altitude affects physiologic responses to myocardial ischemia and infarction. When compared to residents, visitors tended to have more frequent ventricular tachycardia and sinus bradycardia and their blood pressures on admission tended to be higher. Each of these variables could increase oxygen consumption, disrupt the balance of oxygen supply and demand, and be detrimental to ischemic myocardium.

A larger percentage of the visitor population was diagnosed with myocardial infarction in comparison with residents. This important finding suggests that prior to hospitalization, altitude affected the visitor's ability to adequately regulate oxygen supply and demand. When an ischemic event occurred, visitors were less capable of compensating for the oxygen supply and demand imbalance which resulted in a more serious event, myocardial infarction.

These findings plus the extensive literature concerning altitude have implications for nurses. They suggest that even moderate altitude can have a detrimental effect on visitors with coronary heart disease. Until more data is available this knowledge must be used to anticipate and predict patient problems by both the

acute care and community based nurse.

Emergency room and intensive care-coronary care nurses in moderate altitude hospitals and nurse practitioners in isolated clinics have initial contact with visitors presenting with symptoms of coronary heart disease. Their awareness of a possible increased risk of infarction, elevated blood pressures and ventricular tachycardia will promote aggressive nursing care to decrease oxygen demand and preserve myocardium. Appropriate nursing care can decrease risk to visitors by maintaining constant oxygen therapy, and by decreasing sympathetic stimulation by close monitoring of vital signs during activity, limiting social contacts to promote rest and administering sedation as necessary. A routine cardiac activity program may need to be modified to a slower pace for the visitor with coronary artery disease based on nursing observation. Until more data is available concerning the effect of moderate altitude, nurses must classify visitors with coronary artery disease in a high risk category and give nursing care accordingly.

Inservice education for acute care nurses practicing at moderate altitudes concerning the effects of altitude on visitors is essential and will promote appropriate anticipation and prediction in nursing care. Knowledge must be continually updated based on ongoing re-

search in this area.

Both general duty nurses in moderate altitude hospitals and patient health educators at low altitude can educate the visitor or potential visitor to the risks of rapid travel to moderate altitude. Visitors can be taught to recognize signs and symptoms of hypoxia and to modify speed of travel and activity to decrease oxygen consumption and prevent ischemia.

The findings of this study suggest that the community based nurse has as important a role with visitors as the acute care nurse. Since delay in hospitalization may affect morbidity, community groups and local employees who have contact with visitors must be educated concerning the risks of altitude to visitors with coronary artery disease. The Public Health Nurse would be an excellent resource person to organize such an education program.

Working through an active Chamber of Commerce and the National Park Service,the Public Health Nurse could conduct classes focusing on risk, recognition and action surrounding the visitor with coronary artery disease. This would educate the majority of residents coming in contact with visitors. By encouraging residents to anticipate risk and recognize symptoms of coronary artery disease and to facilitate rapid transportation to medi-

cal facilities, the severity of myocardial injury in visitors may be reduced.

The Public Health Nurse could also have an important role in direct education of the visitor through written information. Again, working with the Chamber of Commerce and National Park Service written material describing effects of altitude, symptoms of coronary artery disease, availability and location of medical care, and telephone numbers for ambulance service can be developed. Inclusion of this information with National Park Brochures and availability in all motels, restaurants and businesses could also decrease delay in seeking medical care and reduce the severity of myocardial injury in visitors with coronary artery disease.

Limitations and Recommendations for Further Study

The investigator was aware of several limitations which could have affected results. These were:

1. The possibility of incorrect information documented in the medical records,

2. The inability to verify data in the records,

3. The difficulty in isolating altitude as a causal factor in severity of signs and symptoms in myocardial ischemia and/or infarction in human subjects due to the influence of other variables,

4. The early loss of eleven subjects from the study due to air evacuation or death, and

5. The lack of agreement in the literature concerning the definition of acclimatization altitudes and time periods.

Future research could possibly eliminate the majority of these limitations.

Further investigation of the effects of moderate altitude on visitors and residents with disease is needed. In order to decrease errors in data collection inherent in an ex-post facto chart review, a prospective study should be designed to follow visitors and residents from the onset of their hospitalization. This would allow more accurate measurement of variables such as length of hospitalization and supplemental oxygen usage in units of hours rather than days. Furthermore, information on pre-hospital events including length of time at altitude, speed of travel to altitude, amount of increase in activity from normal lifestyle, and amount of delay from onset of symptoms to medical treatment could be collected. This would allow comparisons of visitors and residents during a period when altitude may have important effects on visitors with coronary artery disease.

Several other variables which were not controlled in this study should be considered in future studies.

Altitude differences between visitors and residents should be greater and more distinct. Instead of including all visitors who reside at altitudes below 1,600 m, only visitors from extremely low altitudes should be compared with residents. This may identify significant variables which were masked in this study by a wider range of visitor altitudes of residence.

A study including large numbers of visitors to the study area who reside at moderate altitudes would be valuable. A comparison between visitors from low altitude, visitors from moderate altitude, and residents could indicate whether moderate altitude actually caused the differences seen in this study, or whether these differences resulted from unknown factors affecting visitors to the study area.

Subjects who are prematurely lost to the study by air evacuation or death should be eliminated from any study variables which are affected by length of hospitalization. This would eliminate skewing of data by short hospital stays which do not indicate patient improvement.

Numerous variables which were insignificant such as admission electrolytes and medication days should be eliminated to make studies more concise. Conversely, pertinent laboratory data such as arterial blood gases

and hemodynamic monitoring data should be collected when possible to allow for comparisons of more subtle and more specific data. Finally, hospitals in different moderate altitude communities should be used for study purposes to eliminate bias caused by the specific attraction a community has for the visitor.

APPENDIX

Coding Sheet

____I.D. #
____Age
____Sex
____Marital Status
____Employment Status
____Visitor/Resident Status
____Altitude of Residence
____Admission Date
____Discharge Date
____Total I.C.C.U. Days

____Diagnosis
____Type of M.I.
____Location of M.I.
____Admission Systolic B.P.
____Admission Diastolic B.P.
____Admission Heart Rate
____Admission Respiratory Rate
____Admission Cardiac Rhythm
____P.V.C.'s on Admission
____B.B.B. on Admission

____Routine Cardiovascular Med
____Family Hx Cardiac Disease
____Hx Cardiac Disease
____Hx Previous M.I.
____Hx Hypertension
____Hx Hyperlipidemia
____Hx Diabetes
____Hx Respiratory Disease
____Hx Cigarette Smoking
____Obesity

____CPK (peak value)
____LDH (peak value)
____Hemoglobin (admission)
____Hematocrit (admission)
____Sodium (admission)
____Potassium (peak value)
____Potassium (lowest value)
____Chloride (admission)
____pH (admission)
____pCO_2 (admission)
____Base Excess (admission)
____TCO_2 (admission)
____HCO_3 (admission)

____Sinus Bradycardia Days
____Sinus Tachycardia Days
____Atrial Flutter Days
____Atrial Fibrillation Days
____Paroxysmal Atrial Tach Days
____Junctional Rhythm Days
____Right B.B.B. Days
____Left B.B.B Days
____1 Degree A-V Block Days
____2 Degree A-V Block Days Type I
____2 Degree A-V Block Days Type II
____3 Degree A-V Block Days
____P.V.C. Days
____Ventricular Escape Rhythm Days
____Ventricular Tachycardia Days
____Ventricular Fibrillation Days
____Cardiac Standstill Days

____Readmission to I.C.C.U.
____Hypotension
____Hypertension
____Cardiomegaly
____Extra Heart Sounds
____Heart Murmur
____Pericarditis
____Thromboembolus
____Congestive Heart Failure
____Extension of Infarction
____Cardiogenic Shock
____Severity of M.I. (Killip's)

____Defibrillation
____Insertion Swan-Ganz Catheter
____Insertion Pacemaker

____Discharged
____Air Evacuated
____Died

____# Supplemental Oxygen Days
____Pain Meds on Admission
____# I.V. Pain Med Days
____# I.V. Antiarrhy. Med Days
____# Oral Antiarrhy. Med Days
____# I.V. Vasoactive Med Days
____# Non-I.V. Vasoactive Med Days
____# I.V. Cardiotonic Med Days
____# Oral Cardiotonic Med Days

REFERENCES

Alexander, J.K., Hartley, L.H., & Modelshi, M. Reduction of stroke volume during exercise in man following ascent to 3100 m altitude. Journal of Applied Physiology, 1967, 23, 849-858.

Alpert, J.S., & Braunwald, E. Pathological and clinical manifestations of acute myocardial infarction. In E. Braunwald (Ed.). Heart disease. Philadelphia: W.B. Saunders, 1980, pp. 1309-1352.

Arias-Stella, J., & Recavarren, S. Right ventricular hypertrophy in native children living at high altitude. American Journal of Pathology, 1962, 41, 55-64.

Arias-Stella, J., & Topilsky, M. Anatomy of the coronary circulation at high altitude. In R. Porter & J. Knight (Eds.). High altitude physiology: Cardiac and respiratory aspects. London: Churchill Livingstone, 1971, p. 149.

Balke, B. Cardiac performance in relation to altitude. American Journal of Cardiology, 1964, 14, 796-810.

Banchero, N., Sime, F., Penaloza, D., Cruz, J., Gamboa, R., & Marticorena, E. Pulmonary pressure, cardiac output, and arterial oxygen saturation during exercise at high altitude and at sea level. Circulation, 1966, 23, 249-262.

Barry, W.H., Brooker, J.Z., Alderman, E.L., & Harrison, D.C. Changes in diastolic stiffness and tone of the left ventricle during angina pectoris. Circulation, 1974, 49, 255-263.

Braunwald, E., & Maroko, P.R. The reduction of infarct size - an idea whose time (for testing) has come. Circulation, 1974, 50, 206-207.

Braunwald, E., & Sobel, B.E. Coronary blood flow and myocardial ischemia. In E. Braunwald (Ed.). Heart disease. Philadelphia: W.B. Saunders, 1980, pp. 1279-1308.

Coffman, J.D., & Greg, D.E. Oxygen metabolism and oxygen debt repayment after myocardial ischemia. American Journal of Physiology, 1961, 201, 881-887.

Cohn, P.F., & Braunwald, E. Chronic coronary artery disease. In E. Braunwald (Ed.). Heart disease. Philadelphia: W.B. Saunders, 1980, pp. 1387-1436.

Comroe, J.H. Physiology of respiration. Chicago: Year Book Medical Publishers, Inc., 1974.

Cummings, G., & Semple, S.J. Disorders of the respiratory system. Oxford: Blackwell Scientific Publications, 1980.

Cunningham, W.I., Becker, F., & Kreuzer, F. Catecholamines in plasma and urine at high altitude. Journal of Applied Physiology, 1965, 20, 607-610.

DeGraff, A.C., Grover, R.F., & Johnson, R.I. Diffusing capacity of the lung in Caucasians native to 3100 m. Journal of Applied Physiology, 1970, 29, 71-76.

Duling, B.R. Microvascular responses to alterations in oxygen tension. Circulation Research, 1972, 31, 481-489.

El-Sherif, N., & Lazzara, K. Reentrant ventricular arrhythmias in the late myocardial infarction period. Effect of verapamil and D-600 and role of the "slow channel". Circulation, 1979, 60, 605-615.

Faulkner, J.A., Kollias, J., Favour, C.B., Buskirk, E.R., & Balke, B. Maximum aerobic capacity and running performance at altitude. Journal of Applied Physiology, 1968, 24, 685-691.

Finch, C., & Lenfant, C. Oxygen transport in man. New England Journal of Medicine, 1972, 286, 407-415.

Forster, H.V., Birnbaum, M.L., Reddan, W.G., Thoden, J.S., Grover, R.F., & Rankin, J. Comparison of ventilatory responses to hypoxic and hypercapnic stimuli in altitude sojourning lowlanders, lowlanders residing at altitude and native altitude residents. Federation Proceedings, Federation of American Society for Experimental Biology, 1969, 28, 1274-1279.

Frayser, H., Gray, G.W., & Houston, C.S. Control of the retinal circulation at altitude. Journal of Applied Physiology, 1974, 37, 302-304.

Graham, W.G.B., & Houston, C.S. Short-term adaptation to moderate altitude. Journal of the American Medical Association, 1978, 240, 1491-1494.

Grover, R.F. Adaptation to high altitude. In L.J. Folinsbee (Ed.). Environmental stress. New York: Academic Press, 1978.

Grover, R.F., Vogel, J.H.K., Voigt, G.C., & Blount, S.G. Reversal of high altitude pulmonary hypertension. American Journal of Cardiology, 1966, 18, 928-932.

Guyton, A.C. Textbook of medical physiology. Philadelphia: W.B. Saunders Company, 1980.

Hansen, J., & Evans, W. A hypothesis regarding the pathophysiology of AMS. Archives of Environmental Health, 1970, 21, 666-669.

Hartley, H. Effects of high altitude environment on the cardiovascular system of man. Journal of the American Medical Association, 1971, 215, 241-244.

Hartley, L.H., Alexander, J.K., Modelski, M., & Grover, R.F. Subnormal cardiac output at rest and during exercise in residents at 3,100 m altitude. Journal of Applied Physiology, 1967, 23, 839-848.

Heath, D., & Williams, D.R. Man at high altitude. London: Churchill Livingstone, 1977.

Holloway, N.M. Nursing the critically ill adult. California: Addison-Wesley Publishing Company, 1979.

Houston, C.S. Going high. Burlington, Vermont: The Alpine Club, 1980.

Hultgren, H.N., & Grover, R.F. Circulatory adaptation to high altitude. Annual Review of Medicine, 1968, 19, 119-152.

Hurst, J., & Logue, R. (Eds.). The Heart. New York: McGraw-Hill Books, 1974.

Hurtardo, A. Animals in high altitudes: Resident man. In Handbook of Physiology. Washington: American Physiologic Society, p. 843.

Jackson, F., & Davies, H. The electrocardiogram of the mountaineer at high altitude. British Heart Journal, 1960, 22, 671-685.

Klausen, K. Cardiac output in man in rest and work during and after acclimatization to 3,800 m. Journal of Applied Physiology, 1966, 21, 609-616.

Lenfant, C., & Sullivan, K. Adaptation to high altitude. New England Journal of Medicine, 1971, 284, 1298-1309.

Lenfant, C., Torrance, J.D., & Reynafarje, C. Shift of the O_2-Hb dissociation curve at altitude: Mechanism and effect. Journal of Applied Physiology, 1971, 30, 625-631.

MacDonald, R. Red cell 2, 3-diphosphoglycerate and oxygen affinity. Anesthesia, 1977, 32, 544-553.

Mathey, D., Bleifeld, W., & Franken, G. Left ventricular relaxation and diastolic stiffness in experimental myocardial infarction. Cardiovascular Research, 1974, 8, 583-592.

Marbarger, J.P., Wechsberg, P.H., Pestel, C.V., Vawter, G.F., & Franzblau, S.A. Altitude stress in subjects with impaired cardiorespiratory function. Journal of Aviation Medicine, 1953, 24, 263-301.

McFadden, D.M., Houston, C.S., Sutton, J.R., Powles, A.C.P, Gray, G.W., & Roberts, R.S. High altitude retinopathy. Journal of the American Medical Association, 1981, 245, 581-586.

Morpurgo, G.P., Battaglia, N.D., Carter, G., Modiano, A., & Passi, S. The Bohr effect and red cell 2, 3-DPG and Hb content in Sherpas and Europeans at low and high altitude. Experientia, 1972, 28, 1280-1283.

Moret, P., Covarrubias, E., & Coudert, J. Cardiocirculatory adaptation to chronic hypoxia. Comparative study of coronary flow, myocardial oxygen consumption and efficiency between sea level and high altitude residents. Acta Cardiology, 1972, 27, 283-305.

Needleman, P., Marshall, G.R., & Sobel, B.E. Hormone interactions in the isolated rabbit heart: Synthesis and coronary vasomotor effects of prostaglandins, angiotensins and bradykinin. Circulation Research, 1975, 37, 802-808.

Parker, J.O. Hemodynamic and metabolic changes during myocardial ischemia. Archives of Internal Medicine, 1972, 129, 790-798.

Pugh, L.G. High altitudes. In O. Edholm & A. Bacharac (Eds.). The physiology of human survival. New York: Academic Press, 1965.

Pugh, L.G., Gill, M.B., & Lahiris, A. Muscular exercise at great altitudes. Journal of Applied Physiology, 1964, 19, 431-440.

Reeves, J.T., Grover, R.F., & Cohn, J.E. Regulation of ventilation during exercise at 10,200 ft. in athletes born at low altitude. Journal of Applied Physiology, 1967, 22, 546-554.

Reeves, J.T., Jokl, P., & Cohn, J.E. Performance of olympic runners at altitudes of 7,350 and 5,350 feet. American Review of Respiratory Diseases, 1965, 92, 813-816.

Reite, M., Jackson, D., Cahoon, R.L., & Weil, J.V. Sleep physiology at high altitude. Electroencephalography and Clinical Neurophysiology, 1975, 38, 463-471.

Saltin, B., Grover, R.F., & Blomquist, C.G. Maximal oxygen uptake and cardiac output after two weeks at 4300 m. Journal of Applied Physiology, 1968, 25, 400-409.

Severinghaus, J.W., Mitchell, R.A., Richardson, B.W., & Singer, M.M. Respiratory control at high altitudes suggestive of active transport regulation of CSF pH. Journal of Applied Physiology, 1963, 18, 1155-1166.

Silber, E., & Katz, L. Heart disease. New York: Macmillian Publishing Company, Inc., 1975.

Sime, F., Penaloza, D., Ruiz, L., Gonzales, N., Covarrubias, E., & Postigo, R. Hypoxemia, pulmonary hypertension and low cardiac output in newcomers at low altitude. Journal of Applied Physiology, 1974, 36, 561-565.

Sobel, B.E. Cardiac and noncardiac forms of acute circulatory collapse. In E. Braunwald (Ed.). Heart disease. Philadelphia: W.B. Saunders, 1980, pp. 590-629.

Sobel, B.E., Bresnahan, G.F., Shell, W.E., & Yoder, R.D. Estimation of infarct size in man and its relation to prognosis. Circulation, 1972, 46, 640-648.

Sobel, B.E., & Shell, W.E. Jeopardized, blighted and necrotic myocardium. Circulation, 1973, 47, 215-216.

Vogel, J.A., & Harris, C.W. Cardiopulmonary responses of resting man during early exposure to high altitude. Journal of Applied Physiology, 1967, 22, 1124-1128.

Voors, A.W., & Johnson, W.D. Altitude and arteriosclerotic heart disease mortality in white residents of 99 of the 100 largest cities in the U.S. Journal of Chronic Disease, 1971, 32, 157-162.

West, J.B., Lahiri, S., & Gill, M.B. Arterial oxygen saturation during exercise at high altitude. Journal of Applied Physiology, 1962, 17, 617-621.

Wilson, R. Acute high altitude illness in mountaineers and problems of rescue. Annuals of Internal Medicine, 1973, 78, 421.